ILE 'HOME' ENTERED AT 08:57:20 ON 08 MAR 2001

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'REGISTRY' ENTERED AT 08:57:53 ON 08 MAR 2001
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STRUCTURE FILE UPDATES: 7 MAR 2001 HIGHEST RN 326471-42-5
DICTIONARY FILE UPDATES: 7 MAR 2001 HIGHEST RN 326471-42-5

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

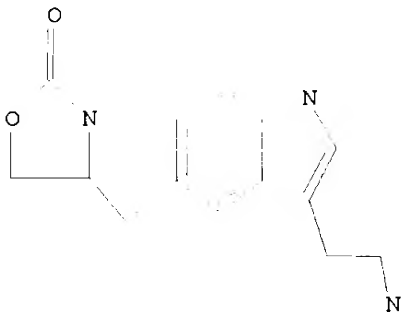
Structure search limits have been increased. See HELP SLIMIT for details.

=>
Uploading 09659683.str

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam

SAMPLE SEARCH INITIATED 08:58:25 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED 2 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

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FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:             2 TO      124
PROJECTED ANSWERS:                2 TO      124

L2            2 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 08:58:32 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     62 TO ITERATE

100.0% PROCESSED      62 ITERATIONS                                42 ANSWERS
SEARCH TIME: 00.00.02

L3            42 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     133.56     133.71

FILE 'CAPLUS' ENTERED AT 08:58:40 ON 08 MAR 2001
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FILE COVERS 1967 - 8 Mar 2001  VOL 134 ISS 11
FILE LAST UPDATED: 7 Mar 2001  (20010307/ED)

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=> s l3 full

L4          122 L3

=> s l4 and migraine?
```

```
          2629 MIGRAINE?
L5          78 L4 AND MIGRAINE?

=> s l5 and headache?

          4183 HEADACHE?
L6          33 L5 AND HEADACHE?
```

=> d l6 1-10 ibib abs hitstr

L6 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:790303 CAPLUS
DOCUMENT NUMBER: 133:329615
TITLE: Device and method using a 5-HT1 agonist for prophylaxis of **migraine**
INVENTOR(S): Cady, Roger K.; Gutterman, Donna Lee; O'Quinn, Stephen
Venson
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

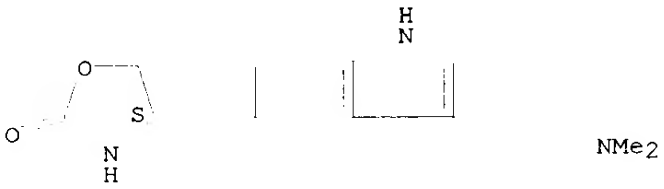
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066115	A1	20001109	WO 1999-US9414	19990429
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9937745	A1	20001117	AU 1999-37745	19990429
PRIORITY APPLN. INFO.:			US 1998-185310	19981103
			WO 1999-US9414	19990429

AB The invention provides a method of preventing the **headache** phase of **migraine** in a human comprising administration of a 5HT1 agonist to said human exhibiting prodrome symptoms of **migraine**. Suitably, the method comprises administration of **migraine** **headache** phase-preventing effective amt. of the 5HT1 agonist. There is disclosed a preemptive prophylaxis **migraine** method using the following cognitive tests: Simple Reaction Time; Running Memory Continuous Performance Task; Matching to Sample; Math. Processing Task; and interprets the results as a percent of baseline indicator of need for prophylaxis. A preemptive prophylaxis **migraine** device including a microprocessor having a memory, a battery of tests loaded into the memory of the microprocessor and including a Simple Reaction Time, a Running Memory Continuous Performance Task, a Matching to Sample, and a Math. Processing Task; means for computing the score on a trial of these tests to establish a baseline and for storing the baseline in the memory; the means for computing being operative for computing the score of a subsequent trial of the tests and comparing the same to the stored baseline; and means for indicating a cognitive change.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(5-HT1 agonist and device for prophylaxis of **migraine**)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

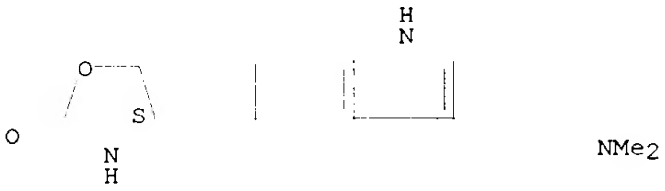
Absolute stereochemistry.



REFERENCE COUNT: 10
REFERENCE(S): (4) Glaxo Group Ltd; EP 0303506 A 1989 CAPLUS
(5) Glaxo Group Ltd; EP 0490689 A 1992 CAPLUS
(6) Glaxo Group Ltd; EP 0503440 A 1992 CAPLUS
(7) Lilly Co Eli; WO 9611006 A 1996 CAPLUS
(8) Merck Sharp & Dohme; EP 0497512 A 1992 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:490411 CAPLUS
DOCUMENT NUMBER: 133:232672
TITLE: Zolmitriptan reverses blink reflex changes induced during the **migraine** attack in humans
AUTHOR(S): de Tommaso, M.; Guido, M.; Libro, G.; Sciruicchio, V.; Puca, F.
CORPORATE SOURCE: Interuniversity Center for the Study of Headache and Neurotransmitter Disorders of the Central Nervous System, Napoli, Florence, Italy
SOURCE: Neurosci. Lett. (2000), 289(1), 57-60
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The question about the 5-hydroxytryptamine (5-HT)1B-1D receptors agonists, if the clin. efficacy in **migraine** attacks is linked with the action at the central level or at the peripheral one, is still unresolved.
We evaluated the effects of zolmitriptan and sumatriptan on blink reflex in thirty **migraine** without aura patients during the attacks in order to assess the central action on the trigeminal system. Both drugs were effective in reducing **headache** severity compared to placebo. In the **migraine** attack an increased area of the R3 component on the pain side was obsd.; it was suppressed by zolmitriptan, which confirmed its action on the central trigeminal circuits, though the clin. relevance of this effect could be questioned.
IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of central trigeminal inhibition, measured by blink reflex changes, in mechanism of antimigraine action of zolmitriptan and sumatriptan in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11
REFERENCE(S): (1) Berardelli, A; Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology, Electroencephalography and Clinical Neurophysiology 1999, V12, P250
(2) Cruccu, G; Brain Res 1991, V556, P209 CAPLUS
(3) Goadbsy, P; Ann Neurol 1988, V23, P193
(6) Humphrey, P; Eur Neurol 1991, V31, P282 MEDLINE
(8) Kaube, H; Br J Pharmacol 1993, V109, P788 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:221634 CAPLUS
DOCUMENT NUMBER: 132:231387
TITLE: **Migraine** pharmacotherapy with oral triptans: a rational approach to clinical management
AUTHOR(S): Millson, David S.; Tepper, Stewart J.; Rapoport, Alan M.
CORPORATE SOURCE: Department of Medicines Management, Keele University, Staffs, ST5 5BG, UK
SOURCE: Expert Opin. Pharmacother. (2000), 1(3), 391-404
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 54 refs. The recent clin. development of a no. of **migraine** specific 5-HT1B/1D agonist triptans with enhanced lipophilicity (TELs), relative to the first drug of this class sumatriptan, and with a range of different metabolic, pharmacokinetic and receptor affinity profiles, provides the potential for critically different clin. profiles. Eletriptan, naratriptan, rizatriptan and zolmitriptan display both increased stability to first pass metabolic inactivation by monoamine oxidase (MAO-A) and enhanced lipophilicity (4- to > 120-fold more than sumatriptan), leading to increased oral bioavailability (2- to 5-fold more than the 14% reported for oral sumatriptan). Central penetration and increased receptor affinity and selectivity for the neuronal (5-HT1D) receptor also combine to allow for lower total oral dosing (i.e., unit doses of 15 mg or less compared with 50 - 300 mg doses of sumatriptan) and reduced peripheral exposure to the coronary vasoconstrictor (5-HT1B) receptor. The notable exception being eletriptan, where an active P-glycoprotein blood-brain barrier efflux system effectively negates these benefits and requires an 80 mg oral dose.

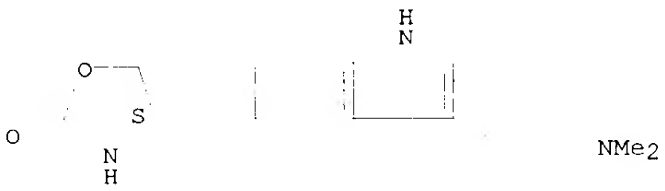
Differences in the metabolic balance between hepatic P 450 (esp. CYP 1A2) and MAO-A inactivation lead to potential drug interactions for all TELs with the oral contraceptive pill (OCP), fluvoxamine and the quinilone antibiotics (with increased triptan levels). An important but complex MAO-A interaction between a metabolite of propranolol and rizatriptan mandates dosage redn. (to 5 mg) for rizatriptan in the presence of propranolol treatment. There is also an abs. contraindication for the concurrent administration of the MAO-A inhibitor moclobemide and rizatriptan. All the new-marketed TELs have potential clin. benefits and were well-tolerated relative to sumatriptan. Both rizatriptan (10 mg) and

zolmitriptan (2.5 mg and 5 mg) demonstrate at least equiv. efficacy to sumatriptan 25, 50 and 100 mg, resp., making them suitable first line agents for moderate or severe **migraine headaches**. Rizatriptan has the fastest onset of effect of the TELs. Naratriptan would appear to have lower recurrent **headache** rate than sumatriptan, rizatriptan or zolmitriptan. Therefore, for **headaches** of long duration and with a tendency to recur naratriptan may be the most appropriate treatment. Thus, knowledge of the metabolic, pharmacokinetic and clin. profiles of the TELs facilitates the selection of a triptan which allows optimization of the clin. benefits for individual patients, minimizing the risk of drug interactions and a minimally ED to reduce potential adverse events (AEs).

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**migraine** pharmacotherapy with oral triptans in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54
REFERENCE(S):
(12) Dixon, C; Biochem Pharmacol 1994, V47, P1253 CAPLUS
(24) Goadsby, P; Pain 1996, V67, P355 CAPLUS
(26) Holm, K; CNS Drugs 1999, V11, P159 CAPLUS
(31) Kramer, M; Neurology 1998, V51, P773 CAPLUS
(35) Millson, D; J Immunol Immunopharmacol 1998, V18, P99 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:220181 CAPLUS
DOCUMENT NUMBER: 132:216448
TITLE: Zolmitriptan in the acute treatment of **migraine**: an overview
AUTHOR(S): Goadsby, Peter J.; Peatfield, Richard
CORPORATE SOURCE: Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London, WC1N 3BG, UK
SOURCE: Rev. Contemp. Pharmacother. (2000), 11(2), 91-97
CODEN: RCPHFW; ISSN: 0954-8602
PUBLISHER: Marius Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

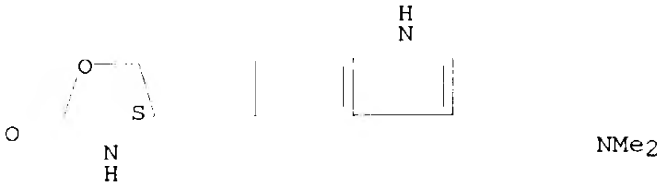
AB A review with .apprx.60 refs. Zolmitriptan is a 5HT1B/1D agonist that is indicated in the acute treatment of **migraine**. Preclin. studies indicate that its potential mechanisms of action include carotid vasoconstriction, inhibition of peripheral terminals of the trigeminal nerve that innervate pain-producing craniovascular structures, or inhibition of trigeminal neurons within the brainstem and upper cervical spinal cord. Clin. pharmacol. studies have demonstrated that zolmitriptan

has a bioavailability of 40% and is largely metabolized in the liver, partly to an active metabolite, N-desmethylzolmitriptan. Zolmitriptan has dose-dependent efficacy across doses from 1 to 25 mg when measured by " **headache** response", in which moderate or severe pain becomes nil or mild, as well as by the "**headache**-free" endpoint. Based on a meta-anal. of the phase II/III placebo-controlled studies, zolmitriptan has, at 2 h after dosing, a **headache** response of 64% (95% Cl: 59-69%) for 2.5 mg and of 66% (95% Cl: 62-70%) for the 5 mg dose. The earliest onset of a significant response when compared to placebo is 45 min after dosing. Zolmitriptan is an effective acute treatment for attacks of **migraine**.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(zolmitriptan in acute treatment of **migraine** in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 85
REFERENCE(S): (13) Dixon, R; Clin Drug Invest 1998, V15, P515 CAPLUS
(15) Dixon, R; J Clin Pharmacol 1998, V38, P694 CAPLUS
(18) Feniuk, W; Br J Pharmacol 1989, V96, P83 CAPLUS
(22) Gaist, D; Br Med J 1998, V316, P1352 CAPLUS
(28) Goadsby, P; CNS Drugs 1998, V10, P271 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:204790 CAPLUS
DOCUMENT NUMBER: 132:217083
TITLE: Efficacy of zolmitriptan at early time-points for the acute treatment of **migraine** and treatment of recurrence: A randomized, placebo-controlled trial
AUTHOR(S): Ryan, Robert E., Jr.; Diamond, Seymour; Giammarco, Rose A. M.; Aurora, Sheena K.; Reed, Ronald C.; Fletcher, Pamela E.
CORPORATE SOURCE: Ryan Headache Center, Chesterfield, MO, USA
SOURCE: CNS Drugs (2000), 13(3), 215-216
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective and Study Design: This double-blind, placebo-controlled trial assessed the efficacy of zolmitriptan vs. placebo at early time-points post-dose as an acute treatment for **migraine** and treatment of **headache** recurrence. Patients and Methods: Patients (18 to 65 yr) with a .gtoreq.1-yr history of **migraine**, age of onset <50 yr and an av. of 2 to 6 **migraine headaches** per mo were recruited by 45 North American research clinics. 1017 Patients were

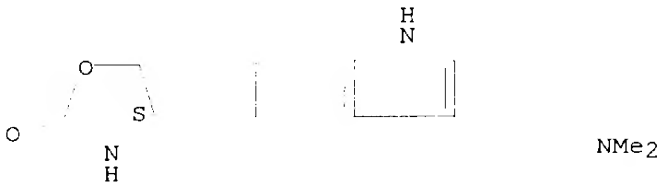
randomized to receive treatment for each of 3 **migraine** **headaches** of moderate or severe baseline intensity (labeled A, B and C, and given in a randomized order). Within each **headache**, patients were randomly allocated to different treatment regimens. Each patient treated each of the 3 **headaches** (A, B and C) with up to 3 doses, i.e. an initial dose (**headache** A, zolmitriptan 2.5mg or placebo; **headache** B, zolmitriptan 5mg or placebo; **headache** C, zolmitriptan 2.5mg), recurrence prevention 8 h after initial dose [**headache** A and B, placebo (to maintain blind); **headache** C, zolmitriptan 2.5mg or placebo] and a recurrence treatment dose, if required (**headache** A and B, zolmitriptan 2.5mg or placebo; **headache** C, zolmitriptan 2.5mg). The 2 primary end-points were **headache** response rates 45 min after the initial dose of zolmitriptan 2.5 or 5mg or placebo, and **headache** response rates 2 h after zolmitriptan 2.5mg or placebo for the treatment of recurrent **headache**, in patients responding at 4 h to the initial dose. Results: A total of 734 patients treated all 3 **headaches**. **Headache** response following an initial dose of zolmitriptan 2.5 and 5mg was significantly greater than placebo by 45 min ($p<0.001$, $p<0.01$, resp.) and was maintained at 1, 2 and 4 h. **Headache** response following zolmitriptan treatment for recurrence was higher than that for placebo, but the difference did not reach statistical significance. A dose taken 8 h after the initial dose did not appear to provide any benefit in preventing recurrent **headache**. Conclusions: Zolmitriptan 2.5 and 5mg provides a rapid onset of action with significant relief of **migraine** **headache** by 45 min post-dose compared with placebo.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of zolmitriptan at early time-points for acute treatment of **migraine** and treatment of recurrence in humans)

RN 139264-17-8 CAPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:98329 CAPLUS
DOCUMENT NUMBER: 132:141982
TITLE: Prevention of **migraine** recurrence
INVENTOR(S): Jackson, Neville Colin; Uden, Stephen
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006161	A1	20000210	WO 1999-IB1105	19990614

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9939521	A1	20000221	AU 1999-39521	19990614
PRIORITY APPLN. INFO.:			GB 1998-16556	19980730
			WO 1999-IB1105	19990614

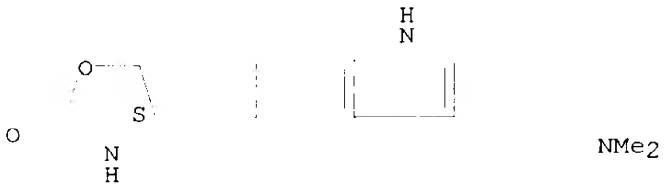
AB The invention relates to the use of eletriptan, or a pharmaceutically acceptable salt or compn. thereof, for the manuf. of a medicament for the prevention of **migraine** recurrence and to the use of a 5-HT1B/1D receptor agonist, or a pharmaceutically acceptable salt or compn. thereof,
for the manuf. of a dual-, sustained-, delayed-, controlled- or pulsed-release pharmaceutical compn. for the prevention of **migraine** recurrence. A clin. example was given showing that eletriptan prevents **migraine** recurrence since when a second dose of eletriptan was administered following successful treatment of an initial **migraine**, the no. of patients experiencing a **migraine** recurrence was at least halved compared with placebo.

IT **139264-17-8**, Zolmitriptan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of **migraine** recurrence with 5-HT1B/1D agonists)

RN 139264-17-8 CAPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7

REFERENCE(S):
(1) Alza Corporation; WO 9912527 A 1999 CAPLUS
(2) Millson, D; EOS RIVISTA IMMUNOLOGIA IMMUNOLOFARMACOLOGIA 1998, V18(3-4), P99 CAPLUS
(3) Pfizer Limited; WO 9901135 A 1999 CAPLUS
(4) Reddy, P; FORMULARY 1998, V33, P521 CAPLUS
(5) Saxena, P; EXPERT OPINION ON INVESTIGATIONAL DRUGS 1996, V5(5), P581 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	2000:92710 CAPLUS
DOCUMENT NUMBER:	132:117519
TITLE:	Zolmitriptan is effective for the treatment of persistent and recurrent **migraine headache**
AUTHOR(S):	Mauskop, Alexander; Farkkila, Markus; Hering-Hanit, Rachel; Rapoport, Alan; Warner, John
CORPORATE SOURCE:	New York Headache Center, New York, 11201, USA
SOURCE:	Curr. Med. Res. Opin. (1999), 15(4), 282-289 CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER:	LibraPharm Ltd.

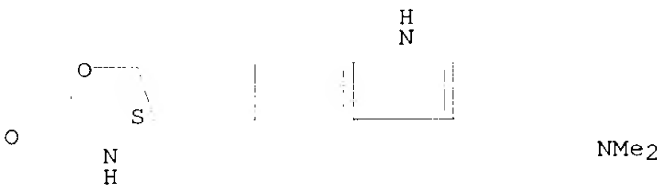
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Zolmitriptan is a 5-HT1B/1D receptor agonist for the acute treatment of **migraine**. This study examd. the efficacy of a second dose of zolmitriptan for the treatment of persistent or recurrent **headache**. Part 1 was a randomized, placebo-controlled, double-blind evaluation of 2.5 mg and 5 mg zolmitriptan for the treatment of persistent **migraine headache**, two hours after an initial dose of 2.5 mg zolmitriptan. In Part 2 (open-label), patients treated the first two attacks with 2.5 mg zolmitriptan, thereafter patients could treat any initial, persistent or recurrent **migraine headache** with 2.5 mg or 5 mg zolmitriptan. The unique design of this trial allowed patients to adjust their treatment to attain max. **headache** relief and control of their disease. Of 2800 patients treating an initial **migraine headache** in Part 1, 989 patients took a second dose to treat persistent **headache** of moderate or severe intensity. **Headache** response rates were similar across the three treatment groups, but the pain-free response rate was significantly higher with 5 mg zolmitriptan than with placebo ($p < 0.001$). In Part 2, 2499 patients treated 49 784 **migraine** attacks (excluding the first two attacks, which had to be treated with 2.5 mg zolmitriptan), of which 66% required only a single dose of zolmitriptan. Patients treated 22% of attacks with a second dose of zolmitriptan for persistent **headache**. A **headache** response was achieved in 80% and 73% of persistent **headaches** treated with 2.5 mg or 5 mg zolmitriptan, resp. Corresponding pain-free responses following treatment of persistent **headaches** of any intensity were 64% and 52%. Eight per cent of attacks were treated with a second dose of zolmitriptan for moderate or severe recurrent **headache**. A **headache** response was achieved in 90% and 86% of moderate/severe attacks, with a pain-free response in 78% and 70% of attacks of any intensity treated with 2.5 mg and 5 mg, resp. Zolmitriptan was well tolerated. In conclusion, 2.5 mg and 5 mg zolmitriptan are highly effective in treating both persistent and recurrent **migraine headache**.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(zolmitriptan is effective for treatment of persistent and recurrent **migraine headache** in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

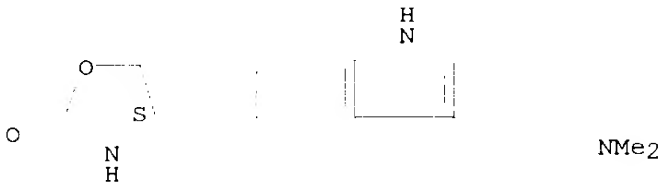


REFERENCE COUNT: 11
REFERENCE(S):
(1) Cull, R; J Neurol Neurosurg Psychiatry 1997, V62, P490 MEDLINE
(5) Mathew, N; Neurol Clin 1997, V15(1), P61 MEDLINE

(7) Rapoport, A; Neurology 1997, V49, P1210 CAPLUS
(9) Solomon, G; Neurology 1997, V49, P1219 CAPLUS
(10) Tepper, S; Curr Med Res Opin 1999, V15(4), P254 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:92709 CAPLUS
DOCUMENT NUMBER: 132:117518
TITLE: Zolmitriptan provides consistent **migraine** relief when used in the long term
AUTHOR(S): Tuchman, Michael; Edvinsson, Larrs; Geraud, Gilles; Korczyn, Amos; Mauskop, Alexander; Pfaffenrath, Volker
CORPORATE SOURCE: Palm Beach Neurological Group, Palm Beach Gardens, FL, 33410, USA
SOURCE: Curr. Med. Res. Opin. (1999), 15(4), 272-281
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Migraine** is a chronic disease that significantly reduces quality of life between, as well as during, attacks. Treatments that provide consistent relief may reduce the burden of the disease. In the open-label phase of a two-part study, patients could choose to treat initial, persistent or recurrent **migraine headache** of any intensity with 2.5 mg or 5 mg zolmitriptan. This novel study design allowed patients to manage and maximize their **migraine** relief. **Headache** response rates and pain-free response rates were assessed within two hours of dosing with zolmitriptan, and response rates were compared across **migraines** with and without a history of aura, and assocd. or not with menses. Consistency of response was also assessed in those patients treating at least 20 attacks. Of 49 784 attacks treated, 66% (32 737 attacks) were treated with a single dose of zolmitriptan. Two-hour **headache** response rates to an initial dose of 2.5 mg or 5 mg zolmitriptan were 85% (median 95%) and 79% (median 88%), resp., across all attacks. Corresponding pain-free response rates were 69% and 59%. Responses were independent of gender and age and were similar in patients with and without aura and in attacks assocd. or not assocd. with menses. Consistent response rates were achieved within individual patients; during months 1 to 3, 64% of patients reported a **headache** response in > 75% of their **migraine** attacks. In patients treating at least 20 attacks, 2.5 mg and 5 mg zolmitriptan produced consistently high **headache** response rates (range 84-91% and 76-84%, resp.) and pain-free response rates (range 70-76% and 58-65%, resp.) across attacks. In the minority of attacks requiring a second dose of zolmitriptan for persistent or recurrent **headache**, response rates to a second dose were also consistent across attacks. In conclusion, zolmitriptan 2.5 mg and 5 mg show consistent effectiveness in the treatment of multiple **migraine** attacks in individual patients and are unaffected by gender, age and the presence of aura or the relationship to menses.
IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zolmitriptan provides consistent **migraine** relief when used in long term in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21
REFERENCE(S):
(1) Clarke, C; Q J Med 1996, V89, P77 MEDLINE
(6) Goadsby, P; Pain 1996, V67, P355 CAPLUS
(13) Rapoport, A; Neurology 1997, V49, P1210 CAPLUS
(16) Solomon, G; Neurology 1997, V49, P1219 CAPLUS
(20) Tepper, S; Curr Med Res Opin 1999, V15(4), P254 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:92708 CAPLUS
DOCUMENT NUMBER: 132:117473
TITLE: A long-term study to maximize **migraine** relief with zolmitriptan
AUTHOR(S): Tepper, Stewart J.; Donnan, Geoffrey A.; Dowson, Andrew J.; Bomhof, Martin A. M.; Elkind, Arthur; Meloche, Jacques; Fletcher, Pamela E.; Millson, David S.
CORPORATE SOURCE: The Polyclinic, Seattle, USA
SOURCE: Curr. Med. Res. Opin. (1999), 15(4), 254-271
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Part 1 of this international study was a randomized, double-blind, placebo-controlled study of 2.5 mg and 5 mg zolmitriptan (Zomig) in the treatment of persistent **migraine headache**, two hours after an initial dose of 2.5 mg zolmitriptan. Part 2 was a non-comparative evaluation of long-term, unrestricted zolmitriptan use for treatment of initial, persistent and recurrent **migraine headaches**. In Part 1, following the treatment of moderate or severe persistent **headache**, two-hour **headache** response rates with 5 mg zolmitriptan (51.6%, n = 322), 2.5 mg zolmitriptan (49.7%, n = 324) and placebo (51.6%, n = 343) were not significantly different. However, the pain-free response rate following the treatment of persistent **migraine headache** of any intensity was significantly higher with 5 mg zolmitriptan than with placebo (36.0% vs. 25.5%; p < 0.001). This was predominantly due to effects in the subgroup of patients with mild **headache**. Thus, **migraine** relief in patients whose initial **headache** shows a partial response to 2.5 mg zolmitriptan may be maximized by a second 5 mg dose. In Part 2 (involving 2499 evaluable patients), 65.8% of attacks were treated with a single dose of zolmitriptan (2.5 mg or 5 mg). Of those **migraine** attacks initially treated with 2.5 mg zolmitriptan, 70.3% required no further dose, similarly 62.7% of **migraine** attacks treated initially with 5 mg zolmitriptan only required a single dose. Over the whole attack (i.e. initial and any persistent **headache**), **headache**

response rates to one or two zolmitriptan doses were greater than 88.8%. "Level of pain" was the primary factor influencing the choice of dose. Zolmitriptan provided consistent **migraine headache** relief in the majority of patients and was well tolerated.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(a long-term study to maximize **migraine** relief with zolmitriptan)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT: 9
REFERENCE(S):
(1) Dixon, R; Cephalalgia 1997, V17(Suppl 18), P15
(2) Edmeads, J; Cephalalgia 1997, V17(Suppl 18), P41
(3) Goadsby, P; Pain 1996, V67, P355 CAPLUS
(4) Headache Classification Committee Of The International Headache Society; Cephalalgia 1988, V8(Suppl 7), P1
(6) Rapoport, A; Neurology 1997, V49, P1210 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:794038 CAPLUS
DOCUMENT NUMBER: 132:18404
TITLE: The triptans: A summary
AUTHOR(S): Tepper, Stewart J.; Rapoport, Alan M.
CORPORATE SOURCE: Department of Neurology, University of Washington Medical School, Seattle, WA, USA
SOURCE: CNS Drugs (1999), 12(5), 403-417
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

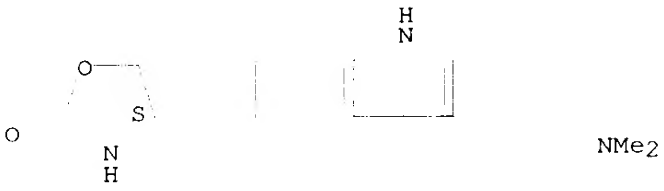
AB A review with 96 refs. New **migraine**-specific medications, the triptans, are changing the clinician's approach to the treatment of **migraine**. These drugs are pharmacol. based on agonism of serotonin (5-hydroxytryptamine; 5-HT) receptors. The triptans are selective 5-HT1B/1D receptor agonists and are believed to reverse the mechanisms of **migraine**, which may include changes in dural vessel calibre, neurogenic inflammation and central trigeminal neuronal activation. The first marketed triptan was sumatriptan. Sumatriptan is available in a highly effective and rapidly active s.c. injectable formulation (optimal dose 6mg), as well as nasal (optimal dose 20mg), oral (optimal dose 50mg) and suppository (optimal dose 25mg) forms. The multiple forms allow for maximal flexibility in crafting an acute care regimen for patients. New triptans are being released in rapid sequence; each new drug has some distinct clin. advantages. All of the triptans released after sumatriptan are more lipophilic and have higher oral bioavailability than sumatriptan. Zolmitriptan was the second marketed

triptan, and is available in oral tablet form (optimal dose 2.5mg). A fast melt prepn. is to be released in Europe in 1999 and a nasal spray form is under development. Zolmitriptan is a well absorbed oral triptan with very high consistency of effect in nonblind studies of over 1 yr in duration. Naratriptan (optimal dose 2.5mg) has a relatively slow onset of action but is assocd. with the lowest **headache** recurrence rate of the currently available triptans. It has a very good adverse event profile with excellent tolerability. Rizatriptan is available as an oral tablet and a rapidly dissolving oral wafer (melt formulation). The optimal dose is 10mg. It is similar to sumatriptan in being an effective oral triptan with a relatively high recurrence rate. Future triptans include eletriptan, which has a very high efficacy in oral form at a dose of 80mg, but a high rate of adverse events at this dose. Lower doses (20 and 40mg) are similar in profile to sumatriptan. Frovatriptan (optimal dose 2.5mg) has an onset of effect and overall efficacy similar to those of naratriptan, but a very low recurrence rate. Almotriptan has the highest oral bioavailability of the triptans. Selection of an acute care **migraine** medication should be based on need for specific delivery form, **headache**- and pain-free response at 2 and 4 h after administration, adverse event profile, consistency of response and recurrence rate. Adverse events for triptans include tightening, flushing and paraesthesias of unknown cause. All triptans cause narrowing of arteries, including coronary arteries, and although serious adverse vascular events are very rare, triptan use is contraindicated in patients with vascular disease.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(triptans for treatment of **migraine** in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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(32) Goadsby, P; CNS Drugs 1998, V10, P271 CAPLUS
(50) Kramer, M; Neurology 1998, V51, P773 CAPLUS
(54) Martin, G; Headache treatment: trial methodology and new drugs 1997, P257 CAPLUS
(56) Mathew, N; Neurology 1997, V49, P1485 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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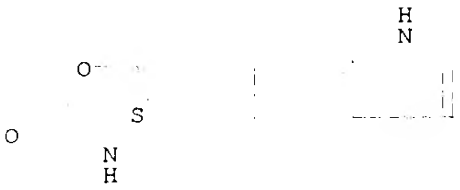
L6 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:594801 CAPLUS
DOCUMENT NUMBER: 131:208393

TITLE: Zolmitriptan: A review of its use in **migraine**
AUTHOR(S): Spencer, Caroline M.; Gunasekara, Nishan S.; Hills, Carol
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (1999), 58(2), 347-374
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 86 refs. Zolmitriptan is a selective serotonin 5-HT1B/1D receptor agonist ("triptan"). Its efficacy and tolerability have been assessed in a no. of randomized, placebo-controlled, double-blind trials in large nos. of adults with moderate to severe **migraine** attacks. Oral zolmitriptan at 2.5 and 5 mg has a rapid onset of action (significant **headache** relief is obtained after 45 min) and efficacy is sustained in most patients who respond at 2 h. The drug is more effective than placebo, as measured by a no. of parameters, including 2-h **headache** response rates and pain-free response rates. Other symptoms of **migraine**, including nausea, photophobia and phonophobia, are also alleviated with zolmitriptan. Zolmitriptan is effective in the treatment of **migraine** assocd. with menses and **migraine** with aura. There is some evidence to support the use of zolmitriptan in patients with **migraine** who have had a poor response to previous therapy. The efficacy of zolmitriptan appears to be maintained, with no tachyphylaxis, following repeated administration for multiple attacks of **migraine** over a prolonged period of time, with high **headache** response rates reported for all attacks. In comparison with placebo, the incidence of persistent **migraine headache** is reduced by zolmitriptan, and recurrent **migraine headache** occurs less frequently with the active treatment. Zolmitriptan has also demonstrated efficacy in the treatment of persistent and/or recurrent **migraine headache**. For relief of **migraine headache**, zolmitriptan at 5 mg had similar efficacy as sumatriptan at 100 mg for a single attack, but it generally was more effective than sumatriptan at 25 and 50 mg for multiple attacks, in single trials. The incidence of recurrent **headache** with zolmitriptan was similar to that with sumatriptan. Zolmitriptan is generally well tolerated, with most adverse events being mild to moderate, transient and resolving without intervention or the need for treatment withdrawal. The most common adverse events with zolmitriptan therapy are asthenia, heaviness other than that of the chest or neck, dry mouth, nausea, dizziness, somnolence, paresthesia, warm sensation, tightness, vasodilation and chest pain. Conclusion: Zolmitriptan is effective across a wide range of **migraine** subtypes, maintains efficacy when used in the long term and is generally well tolerated. Further clin. experience is necessary to define the position of zolmitriptan among other currently or soon to be available selective 5-HT1B/1D receptor agonists. However, on the basis of available data, zolmitriptan should emerge as a useful treatment option in the management of patients with moderate to severe **migraine**.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(zolmitriptan use in human **migraine**)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 86
REFERENCE(S): (7) Dixon, R; Br J Clin Pharmacol 1997, V43, P273 CAPLUS
(11) Dixon, R; Clin Drug Invest 1998, V15, P515 CAPLUS
(14) Dixon, R; J Clin Pharmacol 1998, V38, P694 CAPLUS
(21) Gillotin, C; Int J Clin Pharmacol Ther 1997, V35, P522 CAPLUS
(28) Goadsby, P; Pain 1996, V67, P355 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

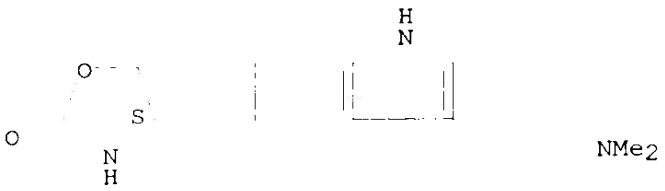
L6 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:466439 CAPLUS
DOCUMENT NUMBER: 131:96701
TITLE: Oral 5-HT1 receptor agonists for **migraine**: comparative considerations
AUTHOR(S): Smith, Melissa A.; Ross, Mary B.
CORPORATE SOURCE: Dep. of Pharmaceutical Care, Univ. of Iowa Hospitals and Clinics, Iowa City, IA, USA
SOURCE: Formulary (1999), 34(4), 324-326, 329-330, 331-332, 335-336, 338
CODEN: FORMF9; ISSN: 1082-801X
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 25 refs. Three new oral 5-HT1 receptor agonists (naratriptan, rizatriptan, and zolmitriptan) have recently joined sumatriptan as options for the treatment of acute **migraine** attacks with or without aura. Currently, the only three published comparative clin. trials use sumatriptan as one of the comparator agents; several other comparative trials exist in abstr. form only. The available data indicate similar efficacy and tolerability among the agents. Sumatriptan offers the advantages of established, long-term safety and efficacy data, few documented drug interactions, no dosage adjustment requirements in patients with renal dysfunction, and availability in injectable and nasal-spray formulations. Naratriptan, because of its longer half-life, may prove useful in patients who experience **migraine** recurrence with sumatriptan, rizatriptan, or zolmitriptan. Rizatriptan tablets (regular formulation) offer a reasonable option when time to onset of **headache** relief is not optimal with sumatriptan. Drawing conclusions about the superiority of any one 5-HT1 receptor agonist over the others is difficult because of the scarcity of published comparative trials.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oral 5-HT1 receptor agonists comparison in treatment of **migraine** in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-,

(4S)- (9CI) (CA INDEX NAME)

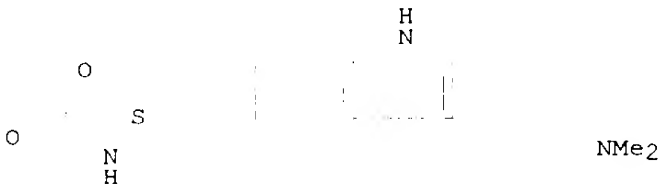
Absolute stereochemistry.



REFERENCE COUNT: 25
REFERENCE(S):
(2) Capobianco, D; Mayo Clin Proc 1996, V71, P1055 MEDLINE
(6) Ferrari, M; Lancet 1998, V351, P1043 MEDLINE
(7) Gijsman, H; Cephalalgia 1997, V17, P647 MEDLINE
(12) Goadsby, P; J Neurol Neurosurg Psychiatry 1998, V64, P143 MEDLINE
(18) Longmore, J; Br J Clin Pharmacol 1996, V42, P431 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:464802 CAPLUS
DOCUMENT NUMBER: 131:251938
TITLE: Pharmacological aspects of experimental **headache** models in relation to acute antimigraine therapy
AUTHOR(S): De Vries, Peter; Villalo, Carlos M.; Saxena, Pramod R.
CORPORATE SOURCE: P.O. Box 1738, Dutch Migraine Research Group and Cardiovascular Research Institute (COEUR), Department of Pharmacology, Erasmus University Medical Centre Rotterdam (EMCR), Rotterdam, 3000 DR, Neth.
SOURCE: Eur. J. Pharmacol. (1999), 375(1-3), 61-74
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with over 150 refs. The last decade has witnessed a tremendous progress in the acute therapy of **migraine**, with sumatriptan, belonging to a new class of drugs, now known as 5-HT1B/1D/1F receptor agonists, leading the way. The undoubted success of sumatriptan stimulated the development of new triptans as well as other suitable pharmacol. tools and exptl. models to probe into complex **migraine** mechanisms. In this review, we discuss the main exptl. models for **migraine**, against the background of the disease pathophysiol. and 5-HT receptors considered most important for **migraine** therapy. We believe that the use of these **migraine** models will provide even better treatment for **migraine** patients in the next millennium.
IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. aspects of exptl. **headache** models in relation to acute antimigraine therapy)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE(S):
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(2) Adham, N; Proc Natl Acad Sci USA 1993, V90, P408 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:257165 CAPLUS
DOCUMENT NUMBER: 131:96735
TITLE: Do we need another triptan for the acute treatment of **migraine headache**?
AUTHOR(S): Millson, D.
CORPORATE SOURCE: Department of Medicines Management, Keele University, Staffordshire, UK
SOURCE: EOS--Riv. Immunol. Immunofarmacol. (1998), 18(3-4), 99-104
CODEN: EOSSDJ; ISSN: 0392-6699
PUBLISHER: Sigma-Tau s.p.a
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

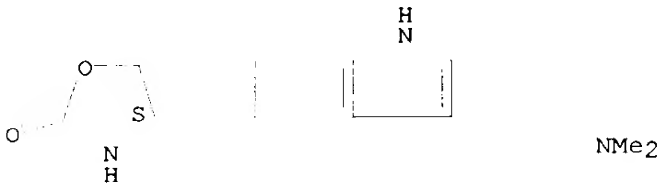
AB A review with 26 refs. Sumatriptan, the first and most extensively studied triptan was a significant therapeutic innovation delivering a high degree of within-patient consistency and robust efficacy with the s.c. formulation; with an extensive range of doses (5,10,25, 50 and 100 mg) across a no. of delivery systems (oral, intra-nasal & rectal). However sumatriptan is hampered by poor oral bioavailability (<14%) due to extensive first pass hepatic metab. limiting its efficacy, and increasing its potential for drug interactions particularly when MAO inhibitors are used a prophylactic agents in **migraine**. Recently Ferrari concluded that "Next generation treatments should aim for greater oral bioavailability assocd. with a faster and more consistent response, a longer duration of action with fewer recurrences, greater selectivity for the carotid vascular bed, less abuse potential, and a lower price". So just how do the new triptans match up to these new challenges All the new triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan) are more lipophilic than sumatriptan (from 4 to >120 fold) have abs. bioavailabilities ranging from 40 to 80%. In addn. both rizatriptan and zolmitriptan have active circulating metabolites which may contribute to clin. activity. The new generation triptans all have increased lipophilicity relative to sumatriptan, which appears to confer enhanced oral bioavailability and CNS penetration. The clin. differences across the triptans in terms of rapidity of onset, efficacy and recurrence rates allows the physician greater choice, enabling therapy to be tailored to the needs of the individual patient.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treatment of **migraine headache** with newer triptans with improved lipophilicity and bioavailability)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26
REFERENCE(S): (3) Cook, R; BMJ 1995, V310, P452 MEDLINE
(15) Perry, C; Drugs 1998, V55, P889 CAPLUS
(17) Rapoport, A; Neurology 1997, V49, P1210 CAPLUS
(19) Solomon, G; Neurology 1997, V49, P1219 CAPLUS
(24) Tfelt-Hansen, P; Lancet 1995, V346, P923 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:167165 CAPLUS
DOCUMENT NUMBER: 131:13798
TITLE: Characterization of the 5-HT receptor binding profile of eletriptan and kinetics of [3H]eletriptan binding at human 5-HT1B and 5-HT1D receptors
AUTHOR(S): Napier, Carolyn; Stewart, Michael; Melrose, Heather; Hopkins, Brian; McHarg, Aileen; Wallis, Rob
CORPORATE SOURCE: Department of Discovery Biology, Pfizer Central Research, Kent, Sandwich, CT13 9NJ, UK
SOURCE: Eur. J. Pharmacol. (1999), 368(2/3), 259-268
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

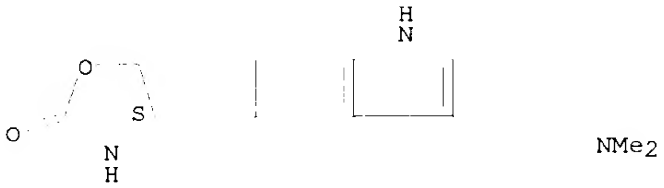
AB The affinity of eletriptan ((R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole) for a range of 5-HT receptors was compared to values obtained for other 5-HT1B/1D receptor agonists known to be effective in the treatment of **migraine**. Eletriptan, like sumatriptan, zolmitriptan, naratriptan and rizatriptan had highest affinity for the human 5-HT1B, 5-HT1D and putative 5-HT1f receptor. Kinetic studies comparing the binding of [3H]eletriptan and [3H]sumatriptan to the human recombinant 5-HT1B and 5-HT1D receptors expressed in HeLa cells revealed that both radioligands bound with high specificity (>90%) and reached equil. within 10-15 min. However, [3H]eletriptan had over 6-fold higher affinity than [3H]sumatriptan at the 5-HT1D receptor (KD: 0.92 and 6.58 nM, resp.) and over 3-fold higher affinity than [3H]sumatriptan at the 5-HT1B receptor (KD: 3.14 and 11.07 nM, resp.). Assocn. and dissocn. rates for both radioligands could only be accurately detd. at the 5-HT1D receptor and then only at 4.degree.. At this temp., [3H]eletriptan had a significantly faster assocn. rate (Kon 0.249 min-1 nM-1) than [3H]sumatriptan (Kon 0.024 min-1 nM-1) and a significantly slower off-rate (Koff 0.027 min-1 compared to 0.037 min-1 for [3H]sumatriptan). These data indicate that eletriptan is a potent ligand at the human 5-HT1B, 5-HT1D and 5-HT1f receptors and are consistent

with its potent vasoconstrictor activity and use as a drug for the acute treatment of **migraine headache**.

IT **139264-17-8**, Zolmitriptan
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(characterization of 5-HT receptor binding profile of eletriptan and kinetics of [3H]eletriptan binding at human 5-HT1B and 5-HT1D receptors
in relation to other 5-HT agonists and vasoconstrictor activity and **migraine headache** treatment)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 52
REFERENCE(S):
(1) Bach, A; J Receptor Res 1993, V13(1-4), P479 CAPLUS
(3) Bard, J; Naunyn-Schmiedeberg's Arch Pharmacol 1996, V354, P237 CAPLUS
(4) Bonhaus, D; Br J Pharmacol 1995, V115, P622 CAPLUS
(6) Cheng, Y; Biochem Pharmacol 1973, V22, P3099 CAPLUS
(8) De Vry, J; Psychopharmacology 1995, V121, P1 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:129095 CAPLUS
DOCUMENT NUMBER: 130:347246
TITLE: Vasoconstriction in human isolated middle meningeal arteries: determining the contribution of 5-HT1B- and 5-HT1F-receptor activation
AUTHOR(S): Razzaque, Z.; Heald, M. A.; Pickard, J. D.; Maskell, L.; Beer, M. S.; Hill, R. G.; Longmore, J.
CORPORATE SOURCE: Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Harlow, CM20 2QR, UK
SOURCE: Br. J. Clin. Pharmacol. (1999), 47(1), 75-82
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

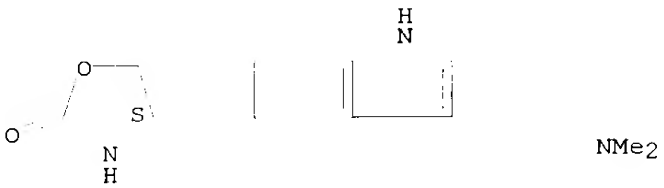
AB Sumatriptan is a 5-HT1B/1D-receptor agonist which also has affinity for 5-HT1F-receptors. The vasoconstrictor effects of sumatriptan are thought to be 5-HT1B-receptor mediated and these receptors have been shown to be expressed in human cranial blood vessels. However, in the same tissue mRNA coding for 5-HT1F-receptors has also been identified and this study addresses the possibility of whether 5-HT1F-receptor activation contributes to vasoconstriction. The ability of two selective 5-HT1B/1D-receptor antagonists (GR125,743 and GR127,935) with no affinity for 5-HT1F-receptors, to inhibit sumatriptan evoked contractions in human isolated middle meningeal artery was investigated. Using a series of 5-HT1B/1D-receptor agonists (sumatriptan, zolmitriptan, CP122,288, L-741,519 and L-741,604), some with high affinity for 5-HT1F-receptors and

the non-selective 5-HT-receptor agonists 5-HT and 5-CT, the authors compared the vasoconstrictor potency of these drugs in human isolated middle meningeal artery with their affinities at cloned human 5-HT1B-, 5-HT1D-and 5-HT1F-receptors expressed in CHO cell lines. GR125,743 antagonized sumatriptan evoked contractions in a competitive manner (apparent pA2 9.1) and GR127,935 antagonized sumatriptan-induced responses in a non-competitive manner (reducing the max. contraction to 27%). There was a significant correlation between vasoconstrictor potency and 5-HT1B-receptor affinity (r=0.93) but not with 5-HT1D- or 5-HT1F-receptor affinity (r=0.74,; r=0.31, resp.). These expts. show that in human middle meningeal artery vasoconstriction to sumatriptan-like agents is 5-HT1B-receptor mediated with little if any contribution from 5-HT1F-receptor activation. The results are discussed in relation to the treatment of **migraine headaches** with serotonin agonists.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(vasoconstriction in human isolated middle meningeal arteries from sumatriptan-like serotonin agonists and detg. the contribution of 5-HT1B- and 5-HT1F-receptor activation in relation to **migraine headache** treatment)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34
REFERENCE(S):
(4) Buzzi, M; Br J Pharmacol 1990, V99, P202 CAPLUS
(5) Clitherow, J; J Med Chem 1994, V37, P2253 CAPLUS
(7) Connor, H; Migraine: Pharmacology and Genetics 1996, P18 CAPLUS
(11) Hamel, E; Mol Pharmacol 1993, V44, P242 CAPLUS
(12) Humphrey, P; Trends Pharmacol Sci 1991, V12, P444 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:401358 CAPLUS
DOCUMENT NUMBER: 129:156990
TITLE: Serotonin 5-HT1B/D receptor agonists
AUTHOR(S): Martin, Graeme R.
CORPORATE SOURCE: Institute of Pharmacology, Roche Bioscience, Palo Alto, CA, USA
SOURCE: Drugs Pharm. Sci. (1998), 89(Receptor-Based Drug Design), 173-194
CODEN: DPHSDS; ISSN: 0360-2583
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

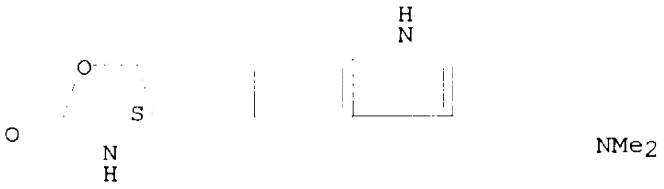
AB A review with 73 refs. discussing the therapeutics of serotonin receptor agonists, esp. for the treatment of **migraines** and **headaches**. The author specifically highlights the drugs sumatriptan and zolmitriptan.

IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serotonin 5-HT1B/D receptor agonists as therapeutics)

RN 139264-17-8 CAPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:276552 CAPLUS

DOCUMENT NUMBER: 129:46

TITLE: Zolmitriptan: a new acute treatment for **migraine**

AUTHOR(S): Rolan, P. E.; Martin, G. R.

CORPORATE SOURCE: Dep. of Neurol., Manchester Royal Infirmary, Manchester, UK

SOURCE: Expert Opin. Invest. Drugs (1998), 7(4), 633-652
CODEN: EOIDER; ISSN: 1354-3784

PUBLISHER: Ashley Publications

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

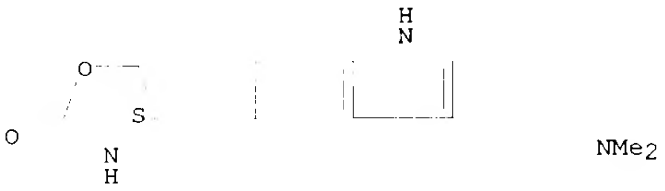
AB A review with 93 refs. Zolmitriptan is a new oral acute treatment for **migraine**. It is a selective and potent agonist at the serotonin (5-HT)1B/1D receptor and was developed to improve on the oral bioavailability, tissue selectivity and CNS penetration of earlier compds.

Animal studies confirmed that these objectives had been attained. In man, zolmitriptan is rapidly absorbed after oral administration, with at least 75% of the eventual Cmax reached within 1 h. Oral bioavailability is approx. 40%. The elimination half-life of zolmitriptan is approx. 2.5 h and the primary route of elimination is metab., with one of the metabolites being pharmacol. active. A consistent 2-h **headache** response rate of 60-70% was obsd. at doses of 2.5 mg and above. Long-term treatment response is high (>80%) and consistent. In addn., there is evidence from electrophysiol. in **migraineurs** that zolmitriptan has a central action not shared by sumatriptan. Zolmitriptan is well-tolerated. The nature and incidence of the most frequently reported adverse events are similar to those of other 5-HT1B/1D agonists. Long-term zolmitriptan usage was assocd. with an improvement in quality of life. Zolmitriptan is a suitable first-line drug for acute treatment for **migraine**.

IT **139264-17-8**, Zolmitriptan:
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(zolmitriptan for acute treatment **migraine** in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



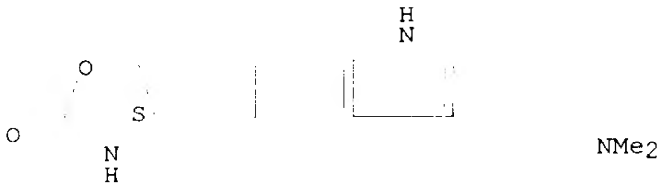
L6 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:66111 CAPLUS
DOCUMENT NUMBER: 128:145352
TITLE: Inclusion complex containing indole selective serotonin agonist
INVENTOR(S): Penkler, Lawrence John; De Kock, Lueta-Ann; Whittaker, Darryl Vanstone
PATENT ASSIGNEE(S): Farmarc Nederland B.V., Neth.; Dyer, Alison, Margaret; Penkler, Lawrence John; De Kock, Lueta-Ann; Whittaker, Darryl Vanstone
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9802186	A1	19980122	WO 1997-GB1872	19970711
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2257860	AA	19980122	CA 1997-2257860	19970711
CA 2259418	AA	19980122	CA 1997-2259418	19970711
AU 9734551	A1	19980209	AU 1997-34551	19970711
AU 712546	B2	19991111		
CN 1225018	A	19990804	CN 1997-196294	19970711
BR 9710241	A	19990810	BR 1997-10241	19970711
CN 1230123	A	19990929	CN 1997-197767	19970711
JP 2000505090	T2	20000425	JP 1998-505725	19970711
PRIORITY APPLN. INFO.:			ZA 1996-5889	19960711
			WO 1997-GB1872	19970711

AB An inclusion complex comprises (a) an indole selective serotonin (5-HTID) agonist or a pharmaceutically acceptable salt thereof, for example sumatriptan, and (b) unsubstituted or substituted .beta.- or .gamma.-cyclodextrin, for example Me .beta.-cyclodextrin. Pharmaceutical compns. contg. the inclusion complex and the use of the inclusion complex in the treatment of **migraine** and cluster **headaches** are also disclosed. A sumatriptan succinate-Me .beta.-cyclodextrin complex

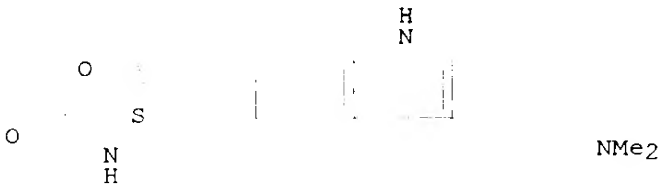
was prepd.
IT **139264-17-8DP**, Zolmitriptan, complexes with cyclodextrin derivs.
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inclusion complex contg. indole selective serotonin agonist)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:778609 CAPLUS
DOCUMENT NUMBER: 128:84344
TITLE: Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of **migraine**
AUTHOR(S): Solomon, G. D.; Cady, R. K.; Klapper, J. A.; Earl, N. L.; Saper, J. R.; Ramadan, N. M.
CORPORATE SOURCE: Cleveland Clinic Foundation, Cleveland, OH, USA
SOURCE: Neurology (1997), 49(5), 1219-1225
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Female and male patients, 12-65 yr old, with **migraine** (with or without aura) for .gtoreq.1 yr, 1-6 **migraines** per mo, and age at onset < 50 yr were included; 327 patients were screened and randomized to receive either zolmitriptan or placebo. Patients treated a single moderate or severe **migraine headache** with 2.5 mg zolmitriptan or placebo and recorded clin. efficacy and adverse events on a diary form. **Headache** response after 2 h was 62% for zolmitriptan compared with 36% for placebo; after 4 h, **headache** response was 70% and 37%, resp. **Headache** recurrence in patients treated with 2.5 mg zolmitriptan was 22% (vs. placebo 30%). The **headache** response after 4 h, pain-free rate, and response rate of nonheadache symptoms favored zolmitriptan over placebo. No serious adverse events were assocd. with zolmitriptan treatment. A 2.5-mg dose of zolmitriptan is clin. effective and well tolerated for the acute treatment of **migraine**.
IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(**migraine** of humans treatment by)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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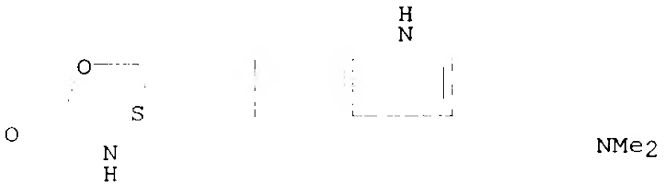
L6 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:778608 CAPLUS
DOCUMENT NUMBER: 128:84343
TITLE: Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of **migraine**. A multicenter, double-blind, placebo-controlled, dose range-finding study
AUTHOR(S): Rapoport, A. M.; Ramadan, N. M.; Adelman, J. U.; Mathew, N. T.; Elkind, A. H.; Kudrow, D. B.; Earl, N. L.
CORPORATE SOURCE: The New England Center for Headache, Stamford, CT, USA
SOURCE: Neurology (1997), 49(5), 1210-1218
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Patients with a history of **migraine** were randomized to receive zolmitriptan orally at 1, 2.5, 5, or 10 mg or placebo for the treatment of a severe or moderate **migraine headache**. Patients with persistent or recurrent **headache** 4-24 h after the initial dose, who did not take escape medication, were eligible to receive a 2nd blinded dose of either zolmitriptan or placebo. The **headache** response rates with zolmitriptan doses .gtoreq.2.5 mg were 44-51% after 1 h, 65-67% after 2 h, and 75-78% after 4 h (all significantly superior to placebo). Also, zolmitriptan effectively relieved **migraine**-assocd. symptoms such as nausea, photophobia and phonophobia, and reduced activity impairment. Rates of **headache** recurrence, **headache** persistence, and use of escape medication were lower with zolmitriptan doses .gtoreq.2.5 mg than with placebo. In patients with persistent or recurrent **headache**, a 2nd zolmitriptan dose effectively treated both **headache** and nonheadache symptoms. Zolmitriptan was well tolerated, with a lower incidence of adverse events being reported with doses .ltoreq.2.5 mg than with those .gtoreq.5 mg. Thus, zolmitriptan is a well-tolerated and effective acute **migraine** therapy providing rapid relief of **migraine headache** within 1 h. A clear dose-response relationship between efficacy and tolerability suggests that 2.5 mg is the optimal initial dose for the acute treatment of a **migraine** attack.

IT **139264-17-8**, Zolmitriptan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(optimum dose of zolmitriptan for the acute treatment of human **migraine**)

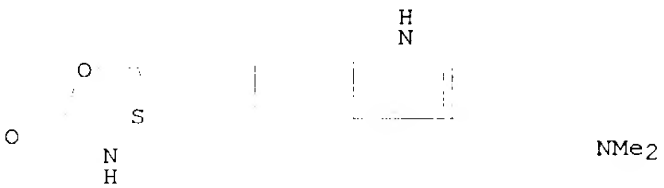
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:437795 CAPLUS
DOCUMENT NUMBER: 127:116915
TITLE: Zolmitriptan
AUTHOR(S): Palmer, Katharine J.; Spencer, Caroline M.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: CNS Drugs (1997), 7(6), 468-479
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 50 refs. Zolmitriptan is indicated for the acute treatment of **migraine** with and without aura. The drug is a serotonin 5-HT1B/1D receptor agonist that has little or no affinity for other serotonin receptors or receptors of other neurotransmitters. Preclin. studies indicate that zolmitriptan has a novel dual mechanism of action, having effects at both central (trigeminal nucleus caudalis) and peripheral (trigeminovascular system) targets. Studies in volunteers demonstrate that zolmitriptan has relatively good oral bioavailability. Zolmitriptan is effective in alleviating **migraine** **headache** and also nonheadache symptoms such as photophobia, phonophobia and nausea. The tolerability of zolmitriptan is good, with the most common adverse experiences being paraesthesia, asthenia, nausea, somnolence and dizziness. Heaviness, tightness or pressure in the chest have been reported, but have not been assocd. with ECG abnormalities.
IT **139264-17-8**, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zolmitriptan therapy for **migraines**)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



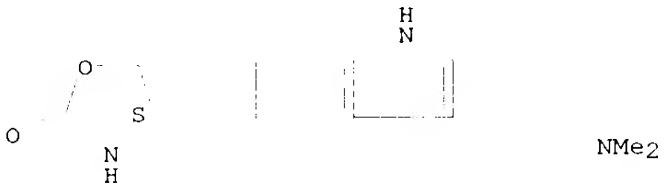
L6 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:237719 CAPLUS
DOCUMENT NUMBER: 126:272250
TITLE: 311C90: long-term efficacy and tolerability profile

for the acute treatment of **migraine**
AUTHOR(S): Zagami, A.S.
CORPORATE SOURCE: Department of Medicine, the St. George Hospital, Sydney, 2217, Australia
SOURCE: Neurology (1997), 48(3, Suppl. 3), S25-S28
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 311C90 (Zomig; zolmitriptan) is a novel, selective serotonin (5HT)1B/1D receptor agonist with both central and peripheral activity, now in late-stage clin. development for acute oral treatment of **migraine**. Several studies have demonstrated the tolerability and efficacy of 311C90 in the treatment of a single **migraine headache**. The objectives of this open-label study were to assess the tolerability and efficacy of repeated doses of 5 mg of 311C90 for acute treatment of multiple attacks for up to 1 yr. Patients were allowed to treat as many **migraine headaches** (mild, moderate, or severe) as desired with an initial dose. A second 5-mg dose could be used to treat recurrence should it develop. Safety assessments included ECG, the frequency, intensity, and duration of adverse experiences, and routine hematol., urinalysis, and clin. chem. parameters. Efficacy assessments included **headache** severity at 2 h (i.e., severe, moderate, mild, or none), the proportion of patients pain-free at 2 h, the use of a second tablet to treat **headache** recurrence if it developed, and the consistency of these findings over time. The efficacy profile and the nature/incidence of adverse events reported appear to be consistent with previous 311C90 studies. The dosing regimen was well tolerated during multiple exposures. Notably, **headache** response rates were consistently good after both initial and repeated exposure (>80% across 1 to 30 attacks). For 67% of patients who treated at least five attacks, 311C90 was effective 80 to 100% of the time.

IT **139264-17-8**, 311C90
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term efficacy and tolerability profile for the acute treatment of **migraine** using 311C90 in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:237718 CAPLUS
DOCUMENT NUMBER: 126:272249
TITLE: 311C90: increasing the options for therapy with effective acute antimigraine 5HT1B/1D receptor agonists
AUTHOR(S): Ferrari, Michel D.
CORPORATE SOURCE: Department of Neurology, Leiden University Hospital, Leiden, 333A, Neth.
SOURCE: Neurology (1997), 48(3, Suppl. 3), S21-S24

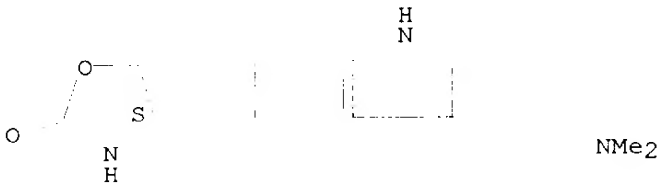
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The novel antimigraine drug 311C90 (Zomig; zolmitriptan) has a high selectivity for serotonin (5HT)1 receptors, mainly 5HT1B and 5HT1D subtypes, and in preclin. studies it has been shown to act on four different sites within the trigemino-vascular system (blockade of neurogenic inflammation by inhibition of peptide release, vasoconstriction, inhibition of neuronal depolarization at peripheral sites, and effects at central sites). Oral 311C90 has a favorable pharmacokinetic profile. It is rapidly absorbed, with 75% of maximal plasma concn. (Cmax) attained within 1 h and good abs. oral bioavailability (approx. 40%). Clin. studies have shown 311C90 to be rapidly and consistently effective in relieving **migraine headache**, with initial doses of between 2.5 and 5 mg providing an optimal balance between efficacy and safety considerations. Moreover, the good tolerability of 311C90 is supported by clin. data showing that doses up to 10-fold the therapeutic dose (2.5 mg) did not raise any serious safety concerns, highlighting the favorable safety profile of this drug.

IT **139264-17-8**, 311C90
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing the options for therapy with 311C90 as an effective acute antimigraine 5HT1B/1D receptor agonist in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:651373 CAPLUS
DOCUMENT NUMBER: 125:317030
TITLE: Can oral 311C90, a novel 5-HT1D agonist, prevent **migraine headache** when taken during an aura?
AUTHOR(S): Dowson, Andrew
CORPORATE SOURCE: Royal and Surrey Research Unit, Royal Surrey County Hospital, Guildford/Surrey, GU2 5XX, UK
SOURCE: Eur. Neurol. (1996), 36(Suppl. 2, 311C90: Further Advances in the Pathogenesis and Acute Treatment of Migraine), 28-31
CODEN: EUNEAP; ISSN: 0014-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

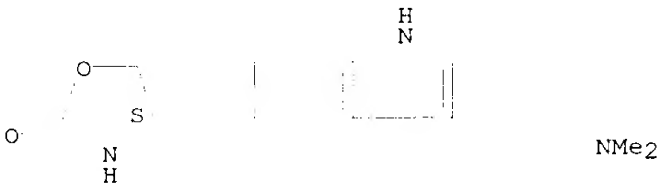
AB The purpose of this pilot study was to det. whether 20 mg oral 311C90 can prevent the development of **migraine headache** when taken during the aura phase of a **migraine** attack. The study also aimed to provide an initial safety profile for 311C90 when taken during the aura. Forty patients (31 females, 9 males) were entered into this outpatient, double-blind, placebo-controlled, 2-period crossover trial. They all almost invariably experienced a **migraine headache** after the aura phase. Patients treated two

migraine attacks during the aura phase in a random order, one with 311C90 20 mg and the other with placebo. Efficacy assessments were recorded on std. diary cards completed by each patient. A primary response was defined as the complete absence of **headache** pain in the 24 h period following administration of the first dose of study medication. Safety assessments included ECGs, lab. tests and the recording of adverse experiences. Twenty patients completed the study by treating 2 attacks, 16 of these were fully adherent to the study protocol.

Three of the 16 patients responded to 311C90 whereas all patients developed a **migraine headache** after taking placebo. Two patients who did not respond to 311C90 described the developing **headache** as being "non-**migraine**". Adverse experiences reported were similar to those experienced by patients in previous studies when 311C90 was taken during a **migraine headache**. There were no reports of 311C90-related adverse effects on the aura. These preliminary results suggest that oral 311C90 may be of value in preventing a **migraine headache** and is safe when taken during the aura phase. This intriguing possibility therefore warrants further investigation possibly utilizing formulations that would deliver meaningful plasma levels of drug more rapidly.

IT **139264-17-8**, 311C90
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral 311C90, a novel 5-HT1D agonist, may prevent **migraine headaches** when taken during an aura in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:651372 CAPLUS
DOCUMENT NUMBER: 125:317029
TITLE: Evaluation of the long-term safety and efficacy of 311C90 in the treatment of **migraine**
AUTHOR(S): Geraud, Gilles E. A.
CORPORATE SOURCE: Service de Neurologie, Hopital Rangeuil, Toulouse, F-31400, Fr.
SOURCE: Eur. Neurol. (1996), 36(Suppl. 2, 311C90: Further Advances in the Pathogenesis and Acute Treatment of Migraine), 24-27
CODEN: EUNEAP; ISSN: 0014-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

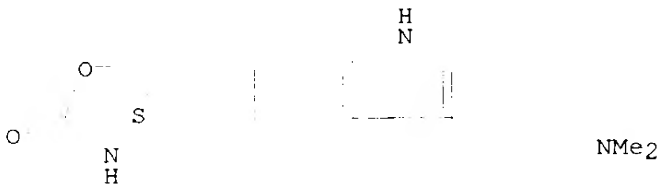
AB 311C90 is an orally active 5-HT1D agonist with both central and peripheral actions that is currently being developed as an acute antimigraine treatment. Several studies have demonstrated the safety and efficacy of 311C90 in the treatment of a single **migraine headache**. The objectives of this open study are to assess the safety and efficacy of 311C90 when used for a period of up to one year. Patients can treat as

many **migraine headaches** as desired with an oral
treatment regimen of 311C90. An initial 5 mg dose for treatment of the **migraine headache** may be followed with a second 5 mg
dose to treat recurrence should it develop. Safety assessments include electrocardiograms, the frequency, intensity and duration of adverse experiences, and routine haematol., urinalysis and clin. chem. measures. Data presented here are an interim view of the database as of August 1995 and should be considered as preliminary observations. No clin. significant serious adverse experiences have been reported. The adverse experience and efficacy profile appears to be consistent with previous 311C90 studies and this dosing regimen of 311C90 was well tolerated during
multiple exposures. Notably, response rates are as good after both initial and repeated exposure (up to 5 **migraines**).

IT **139264-17-8**, 311C90
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(evaluation of the long-term safety and efficacy of 311C90 in the treatment of **migraine** in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:651370 CAPLUS
DOCUMENT NUMBER: 125:292886
TITLE: Inhibition of the trigemino-vascular system with 5-HT1D agonist drugs: Selectively targeting additional sites of action
AUTHOR(S): Martin, Graeme R.
CORPORATE SOURCE: Wellcome Foundation, Beckenham/Kent, UK
SOURCE: Eur. Neurol. (1996), 36(Suppl. 2, 311C90: Further Advances in the Pathogenesis and Acute Treatment of Migraine), 13-18
CODEN: EUNEAP; ISSN: 0014-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

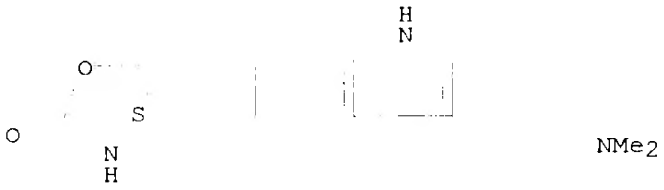
AB Inappropriate activation of the trigemino-vascular system is thought to be important in the pathogenesis of a **migraine** attack. The 5-HT1D agonist sumatriptan, which is highly effective in the acute treatment of **migraine**, inhibits trigemino-vascular activation in animals, although its actions are normally limited to peripheral components of the trigemino-vascular system. 311C90, a novel 5-HT1D agonist drug, which is also highly effective in the acute treatment of **migraine**, acts not only at these sites, but, addnl. within the brainstem, inhibiting trigemino-vascular activation centrally as well as peripherally. This article describes the pre-clin. development of 311C90 and considers, specifically, the approaches taken in the design of a mol. with attributes

which facilitate access to brainstem components of the trigeminal pathway and combine this with good oral bioavailability.

IT **139264-17-8**, 311C90
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibition of trigemino-vascular system with serotoninergic S1D agonists 311C90 and sumatriptan which selectively targeting addnl. sites of action in relation to oral bioavailability and **migraine** attack treatment)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:651369 CAPLUS
DOCUMENT NUMBER: 125:315884
TITLE: Clinical safety of 311C90: Aggregated data from patients and volunteers to date
AUTHOR(S): Earl, Nancy L.
CORPORATE SOURCE: Glaxo Wellcome, Research Triangle Park, NC, 27709, USA
SOURCE: Eur. Neurol. (1996), 36(Suppl. 2, 311C90: Further Advances in the Pathogenesis and Acute Treatment of Migraine), 8-12
CODEN: EUNEAP; ISSN: 0014-3022
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 9 refs. The tolerability of 311C90, a novel, selective and highly effective 5-HT1D receptor agonist in development for the acute treatment of **migraine**, has been evaluated in a no. of clin. pharmacol. and patient studies across the dose range 1-50 mg. 311C90 has been well tolerated across the entire dose range and no clin. relevant changes in routine lab. parameters, blood pressure or ECG recordings have been obsd. Adverse experiences reported are generally dose related, mild to moderate and resolve spontaneously. Chest-related symptoms occur infrequently and the cardiovascular safety profile of 311C90 is considered particularly favorable. 311C90, therefore, possesses a desirable safety profile which is well suited to broad-based outpatient administration.

IT **139264-17-8**, 311C90
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(clin. safety of 311C90 in humans)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

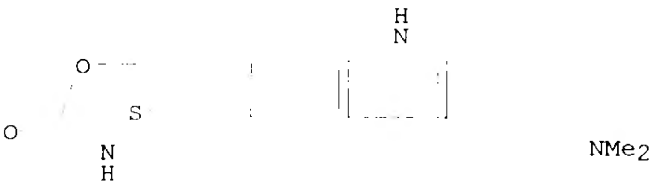
Absolute stereochemistry.

L6 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:651368 CAPLUS
DOCUMENT NUMBER: 125:317028
TITLE: The clinical effectiveness of 311C90 in the acute treatment of **migraine**
AUTHOR(S): Ferrari, Michel D.
CORPORATE SOURCE: Department Neurology, Leiden University Hospital, Leiden, NL-2300, Neth.
SOURCE: Eur. Neurol. (1996), 36(Suppl. 2, 311C90: Further Advances in the Pathogenesis and Acute Treatment of Migraine), 4-7
CODEN: EUNEAP; ISSN: 0014-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Efficacy with currently marketed antimigraine compds. is less than optimal. 311C90 is a novel and selective 5-HT1D receptor agonist in development for the acute treatment of **migraine**. It shows evidence of both central and peripheral activity within the trigemino-vascular system and it is rapidly absorbed following oral administration. In clin. studies in **migraine** patients, a **headache** response at 2 h has been obsd. in 65-81% of patients at doses above 1 mg. Favorable response rates are reported as early as 1 h post-dose and efficacy rates continue to improve up to 4 h. **Headache** recurrence is reported by 25-35% of patients and 311C90 is also effective in relieving the non-**headache** symptoms of **migraine**.

IT **139264-17-8**, 311C90
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(clin. effectiveness of 311C90 in the acute treatment of **migraine** in humans)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:401715 CAPLUS
DOCUMENT NUMBER: 125:67748
TITLE: Methods of treating **migraine** with a tachykinin antagonist and a serotonin agonist
INVENTOR(S): Cohen, Marlene Lois; Johnson, Kirk Willis; Phebus, Lee

Alan
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

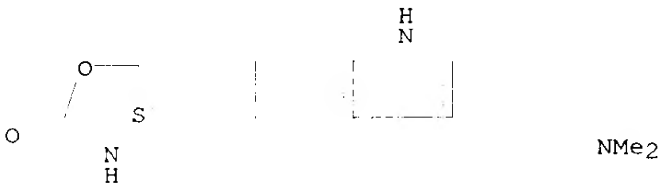
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9611000	A1	19960418	WO 1995-US13087	19951004
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN				
RW: KE, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5744482	A	19980428	US 1994-318391	19941005
EP 710479	A1	19960508	EP 1995-307000	19951003
EP 710479	B1	19990107		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 175347	E	19990115	AT 1995-307000	19951003
ES 2125567	T3	19990301	ES 1995-307000	19951003
AU 9641301	A1	19960502	AU 1996-41301	19951004
PRIORITY APPLN. INFO.:			US 1994-318391	19941005
			WO 1995-US13087	19951004

AB This invention provides methods for the treatment or prevention of **migraines** which comprises administering to a mammal in need thereof a combination of a tachykinin receptor antagonist and a serotonin agonist. This administration may be concurrent or sequential, with either of the two activities being administered first.

IT **139264-17-8**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(methods of treating **migraine** with a tachykinin antagonist and a serotonin agonist)

RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

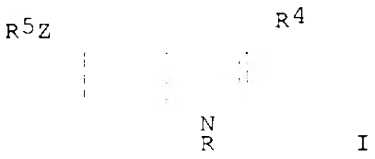


L6 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:175609 CAPLUS
DOCUMENT NUMBER: 124:232432
TITLE: Preparation of indole derivatives as prodrugs of 5-HT1-like receptor agonists
INVENTOR(S): Blade, Robert John; Pang, Yih Sang; Selwood, David Lawrence
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9532966	A1	19951207	WO 1995-GB1249	19950531
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9526219	A1	19951221	AU 1995-26219	19950531
EP 765322	A1	19970402	EP 1995-921004	19950531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10500987	T2	19980127	JP 1995-500520	19950531
US 5962486	A	19991005	US 1996-737759	19961122
PRIORITY APPLN. INFO.:			EP 1994-303928	19940601
			WO 1995-GB1249	19950531

OTHER SOURCE(S): MARPAT 124:232432
GI



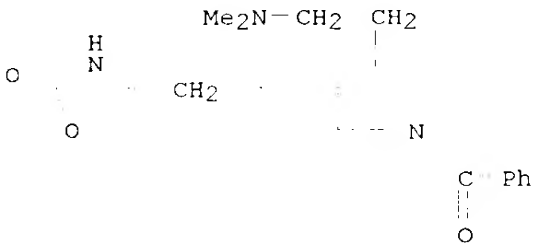
AB Title compds. [I; R = alkanoyl, alkoxycarbonyl, Bz, etc.; R4 = 2-[(di)(alkyl)amino]ethyl, (1-alkyl)-4-piperidinyl, etc.; R5 = 5-oxo-2-pyrrolidinyl, 2-oxo-4-oxazolidinyl, 2,5-dioxo-1-imidazolidinyl, etc.; Z = bond, (CH2)1-3] were prepd. as prodrugs for I (R = H). Thus, I (R4 = CH2CH2NMe2, R5 = 2-oxo-4-oxazolidinyl, Z = CH2)(II; R = Ac) had half-life of .apprx.3h for conversion to II (R = H) in rat plasma.

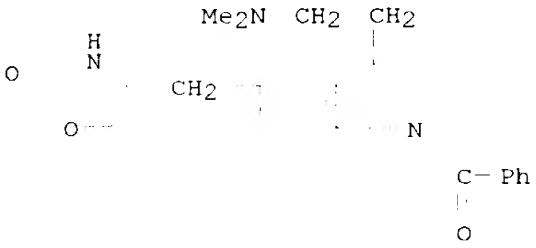
IT **174610-65-2P 174610-67-4P 174610-69-6P**
174610-70-9P 174610-72-1P 174610-74-3P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of indole derivs. as prodrugs of 5-HT1-like receptor agonists)

RN 174610-65-2 CAPLUS
CN 1H-Indole-3-ethanamine, 1-benzoyl-N,N-dimethyl-5-[(2-oxo-4-oxazolidinyl)methyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

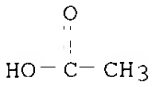
CRN 174610-64-1
CMF C23 H25 N3 O3





CM 2

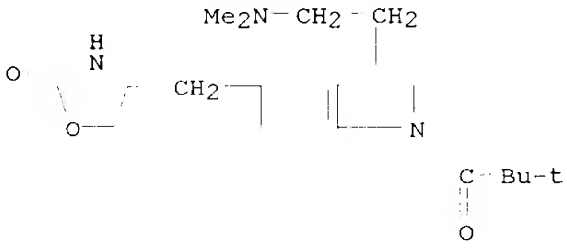
CRN 64-19-7
CMF C2 H4 O2



RN 174610-67-4 CAPLUS
CN 1H-Indole-3-ethanamine, 1-(2,2-dimethyl-1-oxopropyl)-N,N-dimethyl-5-[(2-oxo-4-oxazolidinyl)methyl]-, monoacetate (9CI) (CA INDEX NAME)

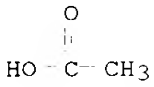
CM 1

CRN 174610-66-3
CMF C21 H29 N3 O3



CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 174610-69-6 CAPLUS
CN 1H-Indole-3-ethanamine, N,N-dimethyl-1-(2-methylbenzoyl)-5-[(2-oxo-4-oxazolidinyl)methyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

CRN 174610-68-5
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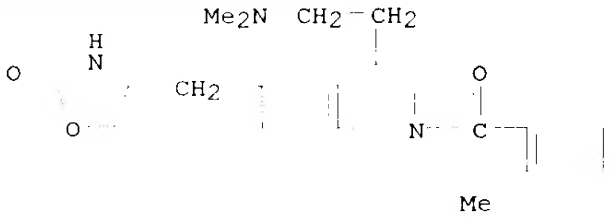
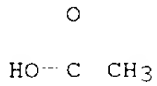
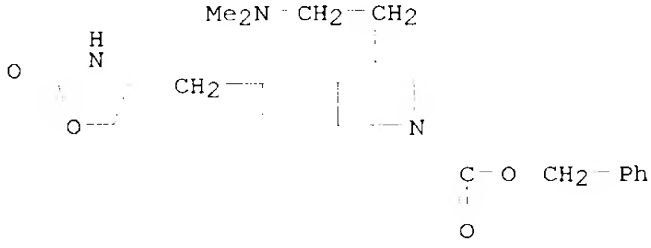


CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 174610-70-9 CAPLUS
CN 1H-Indole-1-carboxylic acid, 3-[2-(dimethylamino)ethyl]-5-[(2-oxo-4-oxazolidinyl)methyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 174610-72-1 CAPLUS
CN 1H-Indole-1-carboxylic acid, 3-[2-(dimethylamino)ethyl]-5-[(2-oxo-4-oxazolidinyl)methyl]-, 1,1-dimethylethyl ester, monoacetate (9CI) (CA INDEX NAME)

CM 1

CRN 174610-71-0
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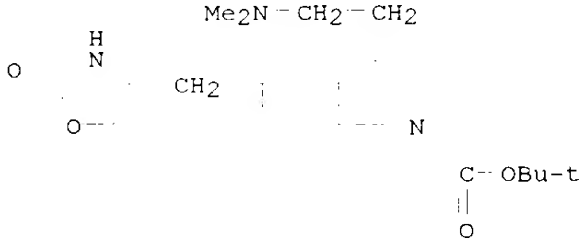
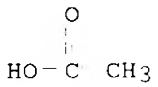


CM 2

CRN 64-19-7

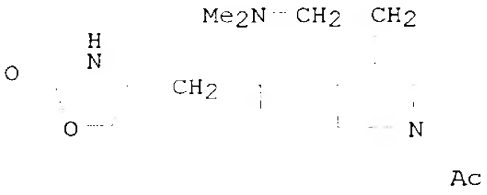
CMF C2 H4 O2



RN 174610-74-3 CAPLUS
CN 1H-Indole-3-ethanamine, 1-acetyl-N,N-dimethyl-5-[(2-oxo-4-oxazolidinyl)methyl]-, monoacetate (9CI) (CA INDEX NAME)

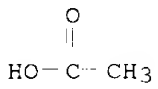
CM 1

CRN 174610-73-2
CMF C18 H23 N3 O3



CM 2

CRN 64-19-7
CMF C2 H4 O2



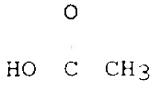
IT **174610-75-4**
RL: RCT (Reactant)
(prepn. of indole derivs. as prodrugs of 5-HT1-like receptor agonists)
RN 174610-75-4 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, monoacetate (9CI) (CA INDEX NAME)

CM 1

CRN 139264-82-7
CMF C16 H21 N3 O2

CM 2

CRN 64-19-7
CMF C2 H4 O2



L6 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:746699 CAPLUS
DOCUMENT NUMBER: 123:132007
TITLE: Computer-Aided Design and Synthesis of 5-Substituted Tryptamines and Their Pharmacology at the 5-HT1D Receptor: Discovery of Compounds with Potential Anti-**Migraine** Properties
AUTHOR(S): Buckingham, Janet; Glen, Robert C.; Hill, Alan P.; Hyde, Richard M.; Martin, Graeme R.; Robertson, Alan D.; Salmon, John A.; Woollard, Patrick M.
CORPORATE SOURCE: Wellcome Research Laboratories, Beckenham/Kent, BR3 3BS, UK
SOURCE: J. Med. Chem. (1995), 38(18), 3566-80
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The design and synthesis of a series of novel 5-substituted tryptamines with pharmacol. activity at 5-HT1D and other monoamine receptors is described. Structural modifications of N- and C-linked (principally hydantoin) analogs at the 5-position were synthesized and their pharmacol. activities were utilized to deduce significant steric and electrostatic requirements of the 5-HT1D and 5-HT2A receptor subtypes. Conformations of the active mols. were computed which, when overlaid, suggested a pharmacophore hypothesis which was consistent with the affinity and selectivity measured at 5-HT1D and 5-HT2A receptors. This pharmacophore is composed of a protonated amine site, an arom. site, a hydrophobic pocket, and two hydrogen-bonding sites. A "selectivity site" was also identified which, if occupied, induced selectivity for 5-HT1D over 5-HT2A in this series of mols. The development and use of the pharmacophore models in compd. design is described. In addn., the physicochem. constraints of mol. size and hydrophobicity required for efficient oral absorption are discussed. Utilizing the pharmacophore model in conjunction with the physicochem. constraints of mol. size and log DpH7.4 led to the discovery of 311C90 (6), a new selective 5-HT1D agonist with good oral absorption and potential use in the treatment of **migraine**.

IT **139264-17-8P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design and synthesis and pharmacol. at 5-HT1D receptor of tryptamine derivs.)
RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

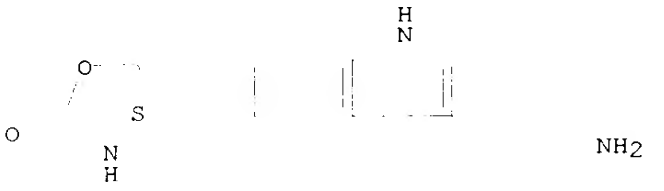
Absolute stereochemistry.

IT **139264-16-7P 139264-24-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(in synthesis of tryptamine derivs.)
RN 139264-16-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, (4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-15-6
CMF C14 H17 N3 O2
CDES 1:S

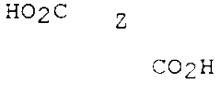
Absolute stereochemistry.



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



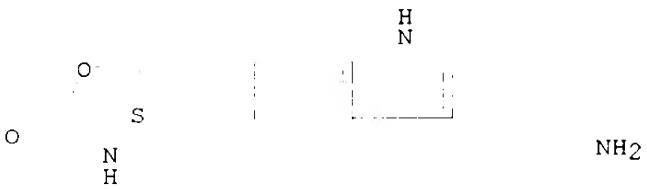
RN 139264-24-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT **139264-15-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)

(in synthesis of tryptamine derivs.)
RN 139264-15-6 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



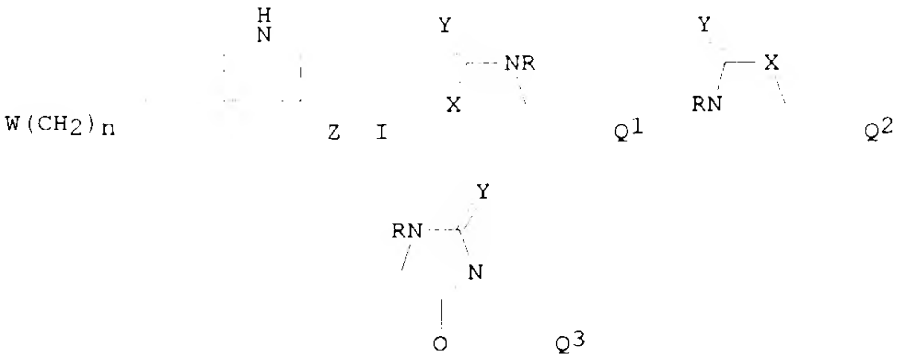
L6 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:174136 CAPLUS
DOCUMENT NUMBER: 116:174136
TITLE: Preparation of [(oxazolidinonylalkyl)indolyl]ethylamines and related compounds as serotonin agonists
INVENTOR(S): Robertson, Alan Duncan; Hill, Alan Peter; Glen, Robert Charles; Martin, Graeme Richard
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9118897	A1	19911212	WO 1991-GB908	19910606
W: AU, BR, CA, FI, HU, JP, KR, MC, NO, PL, SU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2064815	AA	19911208	CA 1991-2064815	19910606
AU 9179570	A1	19911231	AU 1991-79570	19910606
AU 646871	B2	19940310		
EP 486666	A1	19920527	EP 1991-911486	19910606
EP 486666	B1	19970813		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 9104340	A	19930224	ZA 1991-4340	19910606
HU 62289	A2	19930428	HU 1992-384	19910606
JP 05502679	T2	19930513	JP 1991-510103	19910606
JP 2738461	B2	19980408		
EP 636623	A1	19950201	EP 1994-115107	19910606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
PL 166214	B1	19950428	PL 1991-293486	19910606
PL 166799	B1	19950630	PL 1991-305191	19910606
PL 166800	B1	19950630	PL 1991-305192	19910606
IL 98392	A1	19960119	IL 1991-98392	19910606
IL 114690	A1	19970218	IL 1991-114690	19910606
AT 156823	E	19970815	AT 1991-911486	19910606
ES 2104708	T3	19971016	ES 1991-911486	19910606
RU 2110517	C1	19980510	RU 1991-5011473	19910606
NO 9200494	A	19920330	NO 1992-494	19920206
US 5399574	A	19950321	US 1992-838233	19920303
LT 3264	B	19950525	LT 1993-419	19930315
LV 10274	B	19950420	LV 1993-872	19930630
US 5466699	A	19951114	US 1994-341206	19941205
US 5863935	A	19990126	US 1995-471229	19950606

FI 9600155	A	19960112	FI 1996-155	19960112
PRIORITY APPLN. INFO.:			GB 1990-12672	19900607
			GB 1991-2182	19910201
			EP 1991-911486	19910606
			IL 1991-98392	19910606
			WO 1991-GB908	19910606
			FI 1992-503	19920206
			US 1992-838233	19920303
			US 1994-341206	19941205

OTHER SOURCE(S): MARPAT 116:174136

GI



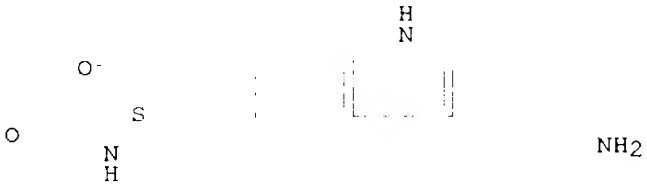
AB Title compds. I [n = 0-3; W = Q1-Q3; R, R1, R2 = H, C1-4 alkyl; X = O, S, NH, CH2; Y = O, S; Z = CH2CH2NR1R2, Q; Q = 4-piperidyl, 1,2,3,6-tetrahydropyridin-4-yl, 1-C1-4 alkyl-4-piperidyl, 1-C1-4 alkyl-1,2,3,6-tetrahydropyridin-4-yl] were prepd. as 5-HT1-like receptor agonists for the treatment of **migraines**. Thus S-4-(4-nitrobenzyl)-1,3-oxazolidin-2-one (prepn. given) was hydrogenated over Pd/C and the product formed was diazotized in the presence of SnCl2 to give the 4-(4-hydrazinobenzyl) deriv. This was cyclocondensed with Cl(CH2)3CH(OMe)2 and the resulting (indolyl)ethylamine deriv. was di-N-methylated by H2CO/NaCNBH3 to give (S)-I [W = Q1; R = H, X, Y = O; n = 1; Z = CH2CH2NMe2] (II). II had p[A50] of 7.0 for mediating smooth muscle contraction where [A50] is the concn. necessary for half-maximal effect. II.HCl orally at 50 mg/kg/day for 15 days was not toxic to cynomolgus monkeys. Formulations of I were prepd.

IT **139264-15-6P 139264-16-7P 139264-17-8P**
139264-18-9P 139264-19-0P 139264-20-3P
139264-21-4P 139264-24-7P 139264-25-8P
139264-28-1P 139264-29-2P 139264-30-5P
139264-31-6P 139264-32-7P 139264-33-8P
139264-34-9P 139264-35-0P 139264-36-1P
139264-82-7P 139346-15-9P 141993-38-6P
141993-39-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as serotonin agonist)

RN 139264-15-6 CAPLUS

CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

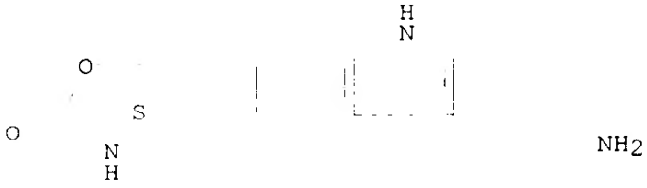


RN 139264-16-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, (4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-15-6
CMF C14 H17 N3 O2
CDES 1:S

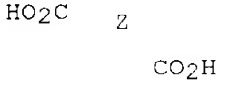
Absolute stereochemistry.



CM 2

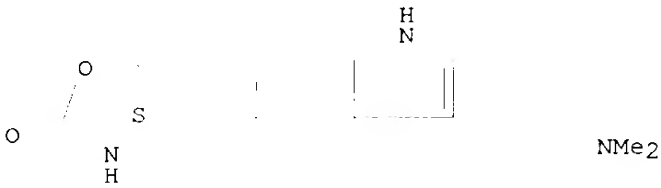
CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



RN 139264-17-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

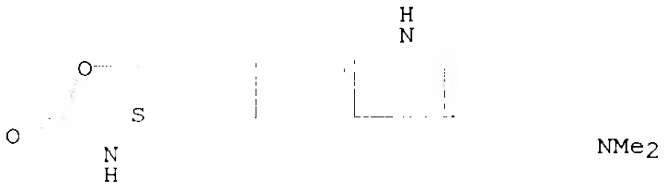


RN 139264-18-9 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-17-8
CMF C16 H21 N3 O2
CDES 1:S

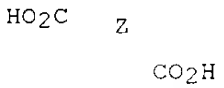
Absolute stereochemistry.



CM 2

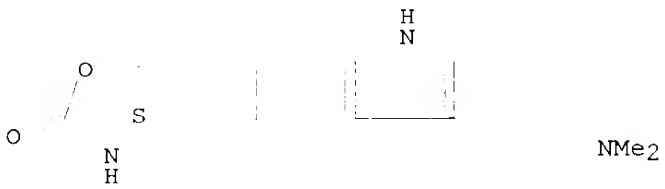
CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



RN 139264-19-0 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, monohydrochloride, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

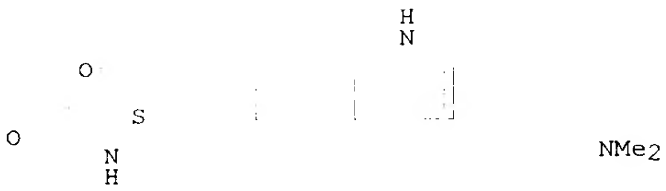


RN 139264-20-3 CAPLUS
CN Butanedioic acid, compd. with (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-17-8
CMF C16 H21 N3 O2
CDES 1:S

Absolute stereochemistry.



CM 2

CRN 110-15-6
CMF C4 H6 O4

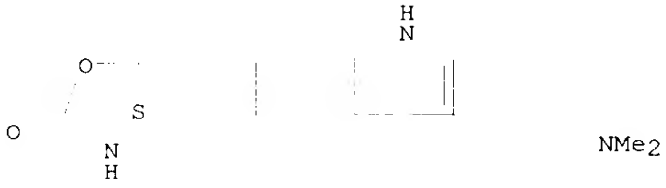
HO_2C CH_2 CH_2 CO_2H

RN 139264-21-4 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (S)-, monobenzoate (9CI) (CA INDEX NAME)

CM 1

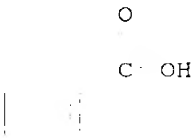
CRN 139264-17-8
CMF C16 H21 N3 O2
CDES 1:S

Absolute stereochemistry.



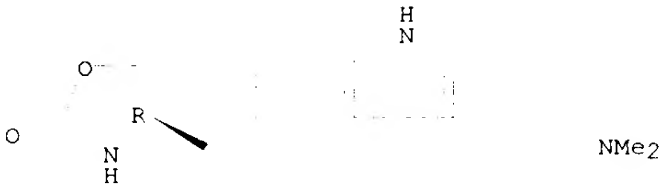
CM 2

CRN 65-85-0
CMF C7 H6 O2



RN 139264-24-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

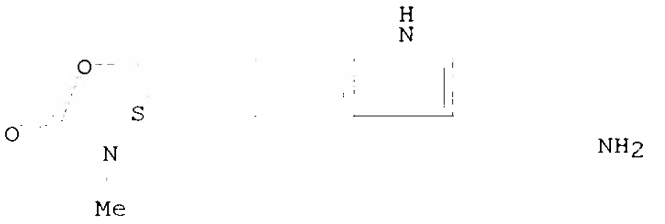


RN 139264-25-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, monohydrochloride, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

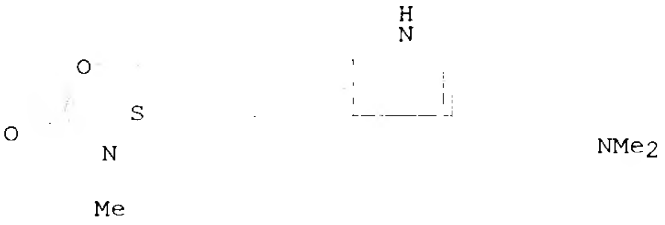
RN 139264-28-1 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-3-methyl-, monohydrobromide, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139264-29-2 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-3-methyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



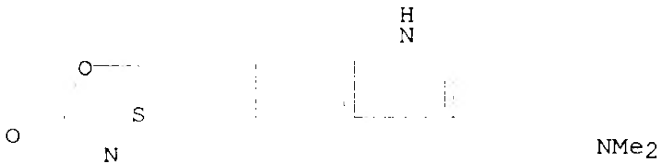
RN 139264-30-5 CAPLUS

CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-3-methyl-, (4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-29-2
CMF C17 H23 N3 O2
CDES 1:S

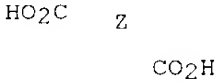
Absolute stereochemistry.



CM 2

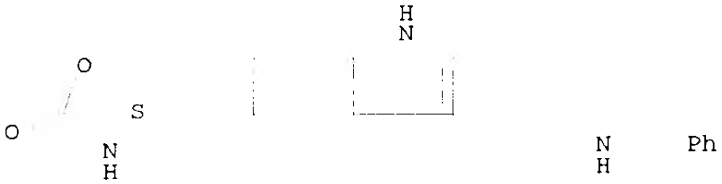
CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



RN 139264-31-6 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-[(phenylmethyl)amino]ethyl]-1H-indol-5-yl]methyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

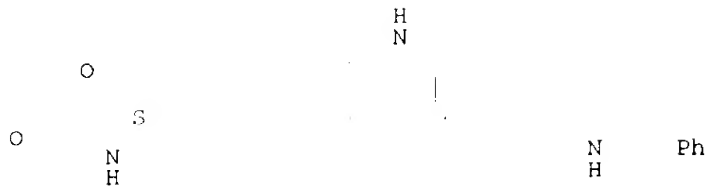


RN 139264-32-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-[(phenylmethyl)amino]ethyl]-1H-indol-5-yl]methyl]-, (4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139264-31-6
CMF C21 H23 N3 O2
CDES 1:S

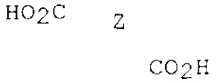
Absolute stereochemistry.



CM 2

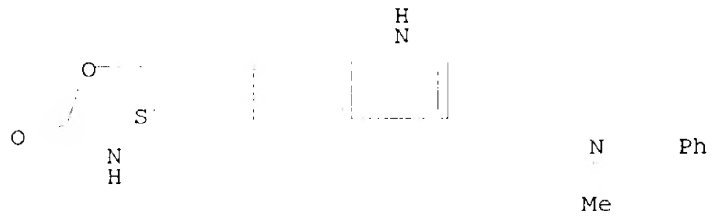
CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



RN 139264-33-8 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-[methyl(phenylmethyl)amino]ethyl]-1H-indol-5-yl]methyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139264-34-9 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-[methyl(phenylmethyl)amino]ethyl]-1H-indol-5-yl]methyl]-, (S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

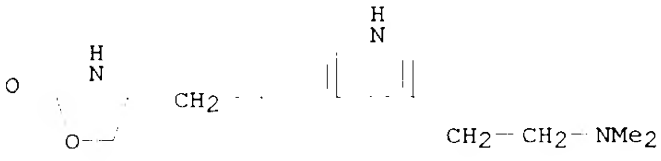
CM 1

CRN 139264-33-8
CMF C22 H25 N3 O2
CDES 1:S

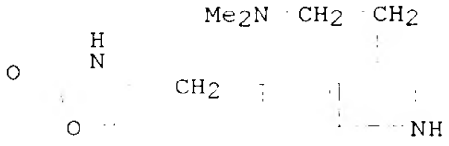
Absolute stereochemistry.

CM 2

(9CI) (CA INDEX NAME)



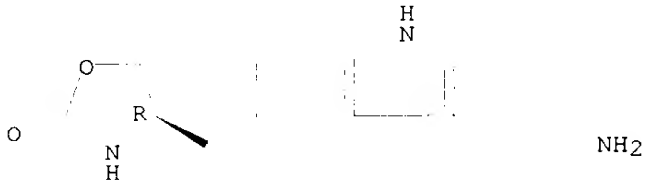
RN 139346-15-9 CAPLUS
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 141993-38-6 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, monohydrochloride, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



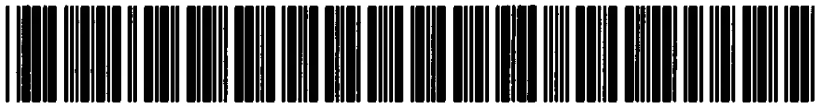
● HCl

RN 141993-39-7 CAPLUS
CN 2-Oxazolidinone, 4-[[3-(2-aminoethyl)-1H-indol-5-yl]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

=>

US 0965968306P1



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No.	Doccode	Number of pages
1	CTNF	6
2	892	1
3	1449	1

Total number of pages: 8

Remarks:

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